## CLAIMS

1. A method for predicting the binding affinity of a peptide for a major histocompatibility (MHC) class I or class II molecule, comprising the following steps:

a) receiving a representation of a complete or partial three-dimensional structure of an MHC class I or class II molecule,

b) obtaining an ensemble of representations of peptide backbone structures of said peptide, said representations located within the binding site of said MHC molecule,

c) modeling for each peptide backbone structure of said ensemble in relation to said MHC molecule, at least the side-chains of said peptide, thereby obtaining an ensemble of modeled MHC/peptide complexes, and

d) evaluating the binding properties of said peptide for said MHC molecule, comprising at least:

d1) evaluating one or more components of the potential energy of each complex of the ensemble,

d2) evaluating the conformational entropy for the complete ensemble.

2. A method according to claim 1 wherein said representation of step (a) is obtained from one of the following:

- one or more experimentally determined structures obtained by for example X-ray crystallography, nuclear magnetic resonance spectroscopy, scanning microscopy, or
- one or more models derived from an experimentally determined structure, whereby said experimentally determined structure has a high sequence identity to said MHC molecule.

3. A method according to claim 1 or 2 wherein said representation of step (b) is generated by a computer modeling method, said method being able to generate multiple energetically favorable backbone configurations in relation to said MHC molecule.

4. A method according to claim 1 or 2 wherein said representation of step (b) is retrieved from a library of peptide structures pre-oriented in relation to said MHC molecule.

5. A method according to any of claims 1 to 4 wherein a complex within said ensemble of step (c) is obtained from a side-chain placement algorithm.

6. A method according to any of claims 1 to 5 wherein the side-chain placement of step (c) not only involves placing the side-chains of the peptide itself, but also involves placing at least one side-chain of said MHC molecule that are in contact with said peptide.

7. A method according to any of claims 1 to 6 wherein a complex within said ensemble of step (c) is obtained from a side-chain placement algorithm suited for global side-chain optimization.

8. A method according to any of claims 5 to 7 wherein the side-chain placement algorithm is a dead-end elimination (DEE) algorithm, characterized in that said DEE algorithm eliminates rotameric conformations on the basis of a mathematical criterion that allows the detection of conformations that are not compatible with the globally optimal conformation.

9. A method according to any of claims 5 to 7 wherein the side-chain placement algorithm is a FASTER algorithm, said algorithm being characterized by a repeated perturbation, relaxation and evaluation step.

10. A method according to any of claims 1 to 9 wherein the binding affinity of step (d) is represented by a single scoring value for the whole ensemble of MHC/peptide complexes, said scoring value comprising the sum of the conformational entropy for the complete ensemble of MHC/peptide complexes, and the average of the said energetical components of each of the complexes of said ensemble.

11. A method according to any of claims 1 to 10 wherein the binding affinity of step (d) is evaluated for the global complex, thereby accounting for interactions between pairs of residues from the peptide, the MHC molecule and both the peptide and the MHC molecule.

12. A method according to any of claims 1 to 11 wherein the entropical component reflects the overall conformational flexibility of the peptide.

13. A method according to any of claims 1 to 12 wherein the representations of said peptide contained in said library are derived from experimentally determined structures.

14. A method according to any of claims 1 to 12 wherein the representations of said peptide contained in said library are derived from computer-generated structures, said structures generated by said computer modeling method of claim 3.

15. A method according to any of claims 1 to 14 wherein said peptide comprises one or more non-naturally occurring amino acids.

16. A method for producing an immunogenic peptide comprising an MHC class I or class II restricted T cell epitope that binds to an MHC class I or class II molecule and induces an MHC class I or II restricted cytotoxic T cell response, said method comprising steps of:

(a) providing an amino acid sequence of a polypeptide of interest;

(b) preparing one or more overlapping putative immunogenic peptide fragments of said polypeptide of interest;

(c) receiving a representation of a complete or partial three-dimensional structure of said MHC class I or class II molecule,

(d) obtaining an ensemble of representations of peptide backbone structures of said putative immunogenic peptides, said representations located within the binding site of said MHC molecule,

(e) modeling for said peptide backbone structures of said ensemble in relation to said MHC molecule, at least the side-chains of said putative immunogenic peptide, thereby obtaining an ensemble of modeled MHC/peptide complexes,

(f) evaluating the binding properties of said putative immunogenic peptides for said MHC molecule, comprising at least:

f1) evaluating one or more components of the potential energy of each complex of the ensemble,

f2) evaluating the conformational entropy for the complete ensemble of each MHC/peptide complex,

(g) inferring from the results obtained in (f), one or more putative immunogenic peptides that bind to said MHC molecule,

(h) optionally preparing one or more of said putative immunogenic peptides of said polypeptide of interest,

(i) optionally testing complexes of said one or more putative immunogenic peptides said MHC molecule for an ability to be recognized by a MHC cytotoxic T cells, and to thereby induce a cytotoxic T cell response to the epitope, and

(e) selecting said one or more putative immunogenic fragments comprising an MHC class I or class II binding site that induce an MHC class I or class II cytotoxic T cell response to the epitope.

17. A method according to claim 16 wherein said representation of step (c) is obtained from one of the following:

- one or more experimentally determined structures obtained by for example X-ray crystallography, nuclear magnetic resonance spectroscopy, scanning microscopy, or
- one or more models derived from an experimentally determined structure, whereby said experimentally determined structure has a high sequence identity to said MHC molecule.

18. A method according to claim 16 or 17 wherein said representation of step (d) is generated by a computer modeling method, said method being able to generate multiple energetically favorable backbone configurations in relation to said MHC molecule.

19. A method according to claim 16 or 17 wherein said representation of step (d) is retrieved from a library of peptide structures pre-oriented in relation to said MHC molecule.

20. A method according to any of claims 16 to 19 wherein a complex within said ensemble of step (e) is obtained from a side-chain placement algorithm.

21. A method according to any of claims 16 to 20 wherein the side-chain placement of step (e) not only involves placing the side-chains of the peptide itself, but also involves placing at least one side-chain of said MHC molecule that are in contact with said peptide.

22. A method according to any of claims 16 to 21 wherein a complex within said ensemble of step (e) is obtained from a side-chain placement algorithm suited for global side-chain optimization.

23. A method according to any of claims 20 to 22 wherein the side-chain placement algorithm is a dead-end elimination (DEE) algorithm, characterized in that said DEE algorithm eliminates rotameric conformations on the basis of a mathematical criterion that allows the detection of conformations that are not compatible with the globally optimal conformation.

24. A method according to any of claims 20 to 22 wherein the side-chain placement algorithm is a FASTER algorithm, said algorithm being characterized by a repeated perturbation, relaxation and evaluation step.

25. A method according to any of claims 16 to 24 wherein the binding affinity of step (f) is represented by a single scoring value for the whole ensemble of MHC/peptide complexes, said scoring value comprising the sum of the conformational entropy for the complete ensemble of MHC/peptide complexes, and the average of the said energetical components of each of the complexes of said ensemble..

26. A method according to any of claims 16 to 25 wherein the binding affinity of step (f) is evaluated for the global complex, thereby accounting for interactions between pairs of residues from the peptide, the MHC molecule and both the peptide and the MHC molecule.

27. A method according to any of claims 16 to 26 wherein the entropical component reflects the overall conformational flexibility of the peptide.

28. A method according to any of claims 16 to 27 wherein the representations of said peptide contained in said library are derived from experimentally determined structures.

29. A method according to any of claims 16 to 28 wherein the representations of said peptide contained in said library are derived from computer-generated structures, said structures generated by said computer modeling method of claim 18.

30. A method according to any of claims 16 to 29 wherein said peptide comprises one or more non-naturally occurring amino acids.

31. A method according to any of claims 1 to 30 wherein said MHC class I molecule comprises an HLA antigen selected from any of the HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G alleles.

32. A method according to any of claims 1 to 30 wherein said MHC class II molecule comprises an HLA antigen selected from any of the HLA-DR, HLA-DQ and HLA-DP gene products.

33. Data comprising

- representations of one or more peptide backbone structures, each peptide demonstrating an interaction with an MHC class I or class II molecule, and
- an indication of the MHC molecule associated with said representation.

34. A computer program comprising computing routines, stored on a computer readable medium for evaluating the binding affinity of a peptide for an MHC class I or class II molecule, said routines comprising:

- receiving an ensemble of representations of structures of the complex between said MHC molecule and said peptide,
- evaluating one or more components of the potential energy of each complex of the ensemble,
- evaluating the conformational entropy for the complete ensemble.

35. A computer program according to claim 34 further comprising modeling for each peptide backbone structure of said ensemble in relation to said MHC molecule, at least the side-chains of said peptide.

36. A computer program according to claim 34 or 35 wherein said peptide backbone structures are obtained by computer modeling or by retrieval from a database.

37. A device for evaluating the binding affinity of a peptide for an MHC class I or class II molecule, comprising:

- receiving an ensemble of representations of structures of the complex between said MHC molecule and said peptide,
- evaluating one or more components of the potential energy of each complex of the ensemble,
- evaluating the conformational entropy for the complete ensemble.

38. A peptide which binds MHC class I or class II molecules, said peptide being obtainable by using the methods of any of claims 1 to 32.

39. An peptide which binds MHC class I or class II molecules, said peptide being obtained by using the methods of any of claims 1 to 32.

40. A nucleic acid encoding a peptide as defined in claim 38 or 39.

41. A nucleic acid of at least 15 nucleotides in length specifically hybridizing with the nucleic acid of claim 40.

42. An antibody specifically recognizing a peptide according to claim 38 or 39.

43. An antibody specifically recognizing a nucleic acid according to claim 40 or 41.

44. A method for producing a peptide according to claims 38 or 39 comprising:

(a) culturing host cells comprising a nucleic acid according to a claim 40 or 41, under conditions allowing the expression of the peptide, and,
(b) recovering the produced peptide from the culture.

45. The peptide according to claim 38 or 39 for use as a medicament.

46. The nucleic acid according to claim 40 or 41 for use as a medicament.